

## Acute coronary syndrome (unstable angina and non-ST elevation MI)

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### ABSTRACT

**INTRODUCTION:** In people with acute coronary syndrome (ACS) the incidence of serious adverse outcomes (such as death, acute myocardial infarction [MI], or refractory angina requiring emergency revascularisation) is 5–10% within the first 7 days and about 15% at 30 days. Between 5–14% of people with acute coronary syndrome die in the year after diagnosis, with about half of these deaths occurring within 4 weeks of diagnosis. **METHODS AND OUTCOMES:** We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of: antiplatelet; antithrombin; anti-ischaemic; lipid-lowering; and invasive treatments? We searched: Medline, Embase, The Cochrane Library, and other important databases up to May 2007 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). **RESULTS:** We found 32 systematic reviews, RCTs, or observational studies that met our inclusion criteria. **CONCLUSIONS:** In this systematic review we present information relating to the effectiveness and safety of the following interventions: aspirin, beta-blockers, calcium channel blockers, clopidogrel, direct thrombin inhibitors, glycoprotein IIb/IIIa inhibitors (oral or intravenous), heparin (low molecular weight, unfractionated), nitrates, routine early cardiac catheterisation and revascularisation, statins, and warfarin.

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### INTERVENTIONS

<b>ANTIPLATELETS</b>		Calcium channel blockers (for MI or death) . . . . .	9
 <b>Beneficial</b>		Nitrates (for MI or death) . . . . .	8
Aspirin . . . . .	3	<b>LIPID-LOWERING TREATMENTS</b>	
Clopidogrel . . . . .	3	 <b>Likely to be beneficial</b>	
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Intravenous glycoprotein IIb/IIIa inhibitors . . . . .	4	<b>INVASIVE TREATMENTS</b>	
<b>ANTITHROMBIN TREATMENTS</b>		 <b>Likely to be beneficial</b>	
 <b>Likely to be beneficial</b>		Routine early cardiac catheterisation and revascularisation . . . . .	10
Direct thrombin inhibitors . . . . .	6	<b>Covered elsewhere in Clinical Evidence</b>	
Low molecular weight heparin . . . . .	5	Acute myocardial infarction	
Unfractionated heparin . . . . .	5	Secondary prevention of ischaemic cardiac events	
 <b>Unlikely to be beneficial</b>		Angina (chronic stable)	
Warfarin . . . . .	7		
<b>ANTI-ISCHAEMIC TREATMENTS</b>			
 <b>Unknown effectiveness</b>			
Beta-blockers (for MI or death) . . . . .	8		

### Key points

- Acute coronary syndrome (ACS, here defined as unstable angina and non-ST elevation MI) is characterised by episodes of chest pain at rest or with minimal exertion, which are increasing in frequency or severity often with dynamic ECG changes.
  - Aspirin** reduces the risk of death, MI, and stroke compared with placebo in people with ACS at doses up to 325 mg daily; higher doses of aspirin are no more effective, and increase the risk of complications.
  - Adding **clopidogrel** to aspirin may reduce the combined outcome of mortality and MI, but may increase the risk of bleeding.
  - Intravenous glycoprotein IIb/IIIa platelet receptor inhibitors** reduce the combined end point of death and MI at 6 months in people with ACS, but increase the risk of bleeding.

Unfractionated or low molecular weight heparin plus aspirin may reduce death or MI at 1 week, but longer-term benefits are unclear.

Low molecular weight heparin may reduce MI compared with unfractionated heparin

Direct thrombin inhibitors (hirudin and bivalirudin) may reduce death or MI compared with unfractionated heparin.

Warfarin has not been shown to be beneficial and increases the risk of major bleeding.

- We don't know whether intravenous nitrates, beta-blockers, or calcium channel blockers reduce the risk of MI or death, although they may reduce the frequency and severity of chest pain.
- CAUTION: Short-acting dihydropyridine calcium channel blockers may increase mortality in people with CHD.
- Early routine cardiac catheterisation and revascularisation may reduce death and non-fatal MI compared with conservative strategies (medical treatment with or without later cardiac catheterisation and revascularisation).

<b>DEFINITION</b>	Acute coronary syndrome (ACS) is term that encompasses unstable angina, non-ST elevation MI (new term for non-Q wave MI, often referred to as non-STEMI), and ST elevation MI (new term for Q wave MI, often referred to as STEMI). Unstable angina and non-STEMI are overlapping entities and will be discussed together in this review. STEMI is discussed elsewhere (see review on acute myocardial infarction). Unstable angina and non-STEMI is a spectrum of disease that involves an imbalance of supply and demand of oxygen available to the myocardium. <sup>[1]</sup> This balance is sometimes disrupted, causing symptoms such as new-onset exertional angina, pre-existing angina that is refractory to nitroglycerin, or angina at rest. The pathophysiology governing anginal symptoms is usually due to atherosclerotic plaque that nearly obstructs coronary vessels. The distinguishing feature between unstable angina and non-STEMI is the presence of elevated cardiac markers such as troponin, which imply myocardial damage. Patient history alone is insufficient to make a diagnosis of ACS. The clinical dilemma of distinguishing between cardiac and non-cardiac pain requires a combination of patient history, ECG, and biomarkers. Overlapping clinical entities in the ACS spectrum of disease allows for similar treatment strategies, and many trials include people with either unstable angina or non-STEMI. We have included systematic reviews and RCTs in a mixed population of people with unstable angina, non-STEMI, or both, which we will refer to here as ACS.
<b>INCIDENCE/ PREVALENCE</b>	In the USA, ACS accounts for more than 1.4 million hospital admissions a year. <sup>[2]</sup> In industrialised countries, the annual incidence of unstable angina is about 6/10,000 people in the general population.
<b>AETIOLOGY/ RISK FACTORS</b>	Risk factors are the same as for other manifestations of ischaemic heart disease — older age, previous atheromatous CVD, diabetes mellitus, smoking, hypertension, hypercholesterolaemia, male sex, and a family history of premature ischaemic heart disease. ACS can also occur in association with other disorders of the circulation, including valvular disease, arrhythmias, and cardiomyopathies. <sup>[1]</sup>
<b>PROGNOSIS</b>	Between 9–19% of people with ACS die in the first 6 months after diagnosis, with about half of these deaths occurring within 30 days of diagnosis. <sup>[3]</sup> Several risk factors may indicate poor prognosis and include severity of presentation (e.g. duration of pain, speed of progression, evidence of heart failure), medical history (e.g. previous ACS, acute MI, left ventricular dysfunction), other clinical parameters (e.g. age, diabetes), ECG changes (e.g. severity of ST segment depression and deep T wave inversion), biomarkers (e.g. presence of troponin concentration elevation), and change in clinical status (e.g. recurrent chest pain, silent ischaemia, haemodynamic instability). <sup>[1]</sup> However, several key prognostic indicators associated with adverse outcomes may be used to aid clinical decision making. Variables including age 65 or over, at least three risk factors for coronary artery disease, known significant coronary stenosis, degree of ST segment deviation, recurrent anginal symptoms in 24 hours, use of aspirin in last 7 days, and elevated cardiac biomarkers can be used to generate a scoring system to predict high-risk patients who may experience true ischaemic cardiac events and death (TIMI [thrombolysis in MI] risk score). <sup>[4]</sup> The more of these factors that are present, the greater the likelihood of adverse ischaemic events. This helps in stratifying patients according to risk, and in identifying high-risk patients.
<b>AIMS OF INTERVENTION</b>	To relieve pain and ischaemia; to prevent death and MI; to identify people at high risk who require revascularisation; to facilitate early hospital discharge in people at low and medium risk; to modify risk factors; to prevent death, MI, and recurrent ischaemia after discharge from hospital, with minimum adverse effects.
<b>OUTCOMES</b>	Mortality, MI, refractory ischaemia or readmission for ACS, adverse effects of treatment.

**METHODS** *Clinical Evidence* search and appraisal May 2007. The following databases were used to identify studies for this systematic review: Medline 1966 to May 2007, Embase 1980 to May 2007, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2007, Issue 2. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and NICE. We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the author for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language, at least single blinded, and containing more than 20 individuals of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as “open”, “open label”, or not blinded unless blinding was impossible. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. We report outcomes of treatment from onset of symptoms up to 6 months in this review. We would also include systematic reviews which combine outcomes from both before and after 6 months. Systematic reviews and RCTs that cover secondary prevention in mixed manifestations of atherosclerotic coronary artery disease are reported in the review on Secondary prevention of ischaemic cardiac events. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 13 ). To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as RRs and ORs.

**QUESTION** What are the effects of antiplatelet treatments in people with acute coronary syndrome?

**OPTION** ASPIRIN

#### Cardiovascular events

*Compared with placebo* Aspirin is more effective at reducing the combined outcome of vascular death, MI, or stroke at 14 days to 18 months in people with unstable angina (*moderate-quality evidence*).

#### Bleeding

*Compared with placebo* Aspirin increases the risk of major extracranial bleeding (*moderate-quality evidence*).

**For GRADE evaluation of interventions for acute coronary syndromes, see table, p 13 .**

#### Benefits:

##### Aspirin versus placebo:

One systematic review (search date 1997, 287 RCTs, 135,000 people) compared antiplatelet treatment versus placebo in people at high risk of vascular events.<sup>[5]</sup> Twelve of the RCTs (5031 people) evaluated people with unstable angina. The review found that antiplatelet treatment in these people (8 RCTs aspirin, 1 RCT aspirin plus dipyridamole, 2 RCTs ticlopidine, 1 RCT triflusal) reduced the combined outcome of vascular death, MI, or stroke compared with placebo at 14 days to 18 months (AR 199/2497 [8%] with antiplatelet treatment v 336/2534 [13%] with placebo; OR 0.54, 95% CI reported graphically; P less than 0.0001). The individual trials from the review that evaluated aspirin alone also found consistent benefit in reduced deaths and MI. The review concluded that, overall, there is no added cardiovascular benefit for aspirin doses greater than 325 mg daily.

#### Harms:

##### Aspirin versus placebo:

The systematic review did not give any information on harms separately from people with unstable angina. Overall, it found that antiplatelet treatment significantly increased major extracranial bleeding compared with placebo, but the absolute risk was low (AR 535/47,158 [1.1%] with antiplatelet treatment v 333/47,168 [0.7%] with placebo; OR 1.6, 95% CI 1.4 to 1.8). It found no significant difference in non-vascular mortality between antiplatelet treatment and placebo (AR 785/71,656 [1%] with antiplatelet treatment v 872/71,876 [1%] with placebo; OR 0.92, 95% CI 0.82 to 1.03).<sup>[5]</sup> Adverse effects are more common with aspirin doses greater than 325mg. Some people have a significant allergy to aspirin.

#### Comment:

Acute coronary syndrome patients who are allergic to or do not respond to aspirin are likely to benefit from alternative antiplatelet treatment.

**OPTION** CLOPIDOGREL

#### Cardiovascular events

*Compared with placebo* Clopidogrel is more effective at reducing the combined outcome of cardiovascular death, MI, or stroke at 30 days in people with acute coronary syndromes ([moderate-quality evidence](#)).

### Bleeding

*Compared with placebo* Clopidogrel increases the risk of major bleeding at 3–9 months in people taking aspirin compared with aspirin plus placebo ([high-quality evidence](#)).

**For GRADE evaluation of interventions for acute coronary syndromes, see [table, p 13](#).**

### Benefits:

#### Clopidogrel versus placebo:

We found one RCT (12,562 people with ACS) comparing clopidogrel (300 mg orally within 24 hours of onset of symptoms followed by 75 mg/day) versus placebo. <sup>[6]</sup> All participants received aspirin (75–325 mg/day). It found that clopidogrel significantly reduced the combined outcome of death from cardiovascular causes, MI, and stroke at 30 days compared with placebo (AR presented graphically; RR 0.82, 95% CI 0.70 to 0.95). <sup>[6]</sup>

### Harms:

#### Clopidogrel versus placebo:

The RCT found that clopidogrel plus aspirin significantly increased major bleeding compared with aspirin alone at 3–9 months, but haemorrhagic stroke was similar in both groups (major bleeding: AR 231/6259 [4%] with clopidogrel v 169/6303 [3%] with placebo; RR 1.4, 95% CI 1.1 to 1.7; haemorrhagic stroke 0.1% with clopidogrel v 0.1% with placebo; RR and 95% CI not reported). <sup>[6]</sup> Post-hoc subgroup analysis showed that increasing aspirin dose increased the risk of major bleeding, with little corresponding reduction in cardiovascular risk. <sup>[7]</sup> The study concluded that the optimum daily dose of aspirin for use in combination with clopidogrel was 75–100 mg. One systematic review (search date 2002) of RCTs of antiplatelet agents for different indications, including acute coronary syndrome, found that the weighted mean rate of major bleeding with ticlopidine or clopidogrel was 2% (95% CI 1.9% to 2.3%; 8 RCTs, 18,574 people) and the rate of minor bleeding was 5% (95% CI 4.6% to 5.7%; 1 RCT, 6259 people). <sup>[8]</sup> Clopidogrel is associated with other adverse effects, including diarrhoea and rash.

### Comment:

Post-hoc subgroup analysis found that the reduction in cardiovascular death, MI, and stroke with clopidogrel was seen across all risk groups (low, medium, and high, as classified by Thrombolysis In MI [TIMI] risk score) of ACS. <sup>[9]</sup> A second post-hoc subgroup analysis found that giving clopidogrel on admission to the hospital did not increase the rate of bleeding requiring transfusion in patients undergoing CABG compared with when clopidogrel was withheld for greater than 5 days. It is therefore recommended that clopidogrel is not withheld in high-risk patients upon admission, unless there is a clear contraindication.

## OPTION

## INTRAVENOUS GLYCOPROTEIN IIB/IIIA PLATELET RECEPTOR INHIBITORS

### Cardiovascular events

*Compared with placebo* Intravenous glycoprotein IIB/IIIA inhibitors may be more effective at reducing the combined outcome of death or MI at 30 days in people with high-risk acute coronary syndrome ([low-quality evidence](#)).

### Bleeding

*Compared with placebo* Intravenous glycoprotein IIB/IIIA inhibitors increase the risk of major bleeding at 30 days ([moderate-quality evidence](#)).

**For GRADE evaluation of interventions for acute coronary syndromes, see [table, p 13](#).**

### Benefits:

#### Intravenous glycoprotein IIB/IIIA inhibitors versus placebo:

We found one systematic review (6 RCTs, 31,402 people) comparing intravenous glycoprotein IIB/IIIA inhibitors versus placebo in people with acute coronary syndrome. <sup>[10]</sup> The participants in all the identified RCTs had ischaemic ECG changes or elevated cardiac enzymes. Routine invasive treatment was not planned for the participants of any of the RCTs. However, 38% of people in the glycoprotein IIB/IIIA inhibitor group and 39% of people in the control group had undergone either percutaneous coronary intervention (PCI) or CABG by day 30. It found that intravenous glycoprotein IIB/IIIA inhibitors (abciximab, eptifibatide, lamifiban, and tirofiban) significantly reduced the combined outcome of death and MI at 30 days (AR 1980/18,297 [11%] with glycoprotein IIB/IIIA inhibitors v 1550/13,105 [12%] with control, OR 0.9, 95% CI 0.84 to 0.98; P = 0.015).

The RCTs identified by the systematic review pre-dated the routine use of thienopyridines. It is uncertain whether the same findings would be seen in patients treated with thienopyridines, or in patients not routinely scheduled for PCI.

- Harms:** **Intravenous glycoprotein IIb/IIIa inhibitors versus placebo:**  
The systematic review found that glycoprotein IIb/IIIa inhibitors significantly increased major bleeding compared with placebo at 30 days (AR 445/18297 [2%] with glycoprotein IIb/IIIa inhibitors v 180/13,105 [1%] with placebo; OR 1.6, 95% CI 1.4 to 1.9). It found no significant difference in stroke between groups at 30 days (AR 137/18297 [1%] with glycoprotein IIb/IIIa inhibitors v 91/13,105 [1%] with placebo; OR 1.11, 95% CI 0.8 to 1.5).
- Comment:** **Clinical guide:**  
Intravenous glycoprotein IIb/IIIa inhibitors are recommended for people with high-risk acute coronary syndrome who do not have active bleeding. There are uncertainties associated with use of intravenous glycoprotein IIb/IIIa inhibitors in people not routinely scheduled to undergo PCI and patients pre-treated with a thienopyridine. In patients who do undergo PCI, heparin should be discontinued after the procedure.

**QUESTION** What are the effects of antithrombin treatments in people with acute coronary syndrome?

**OPTION** UNFRACTIONATED HEPARIN

### Cardiovascular events

*Compared with aspirin alone* Unfractionated heparin plus aspirin may be more effective at reducing the combined outcome of death or MI at 7 days in people with acute coronary syndrome, but seems no more effective at 12 weeks (moderate-quality evidence).

### Bleeding

*Compared with aspirin alone* We don't know what effect unfractionated heparin plus aspirin has on the risk of major bleeding (moderate-quality evidence).

For GRADE evaluation of interventions for acute coronary syndrome, see [table, p 13](#).

**Benefits:** **Unfractionated heparin versus no unfractionated heparin:**  
We found two systematic reviews (search dates 1995<sup>[11]</sup> and not stated<sup>[12]</sup>), examining outcomes at different time points (7 days and 12 weeks). Both included the same six RCTs in 1353 people with acute coronary syndrome who were treated with either unfractionated heparin plus aspirin or aspirin alone for 2–7 days. The first review found that unfractionated heparin plus aspirin reduced the risk of death or MI at 7 days compared with aspirin alone (AR 55/698 [8%] with unfractionated heparin plus aspirin v 68/655 [10%] with aspirin alone; OR 0.67, 95% CI 0.45 to 0.99).<sup>[12]</sup> The second review found that heparin plus aspirin did not reduce death or MI after 12 weeks compared with aspirin alone (AR 12% with unfractionated heparin plus aspirin v 14% with aspirin; RR 0.82, 95% CI 0.56 to 1.20).<sup>[11]</sup>

### Unfractionated heparin versus low molecular weight heparin:

[See benefits of low molecular weight heparin, p 5](#).

**Harms:** **Unfractionated heparin versus no unfractionated heparin:**  
The second systematic review found no significant difference in major bleeding with unfractionated heparin plus aspirin compared with aspirin alone, but reported a wide CI (AR 1.5% with unfractionated heparin plus aspirin v 0.4% with aspirin; RR 1.89, 95% CI 0.66 to 5.38; P = 0.68).<sup>[11]</sup>

### Unfractionated heparin versus low molecular weight heparin:

[See harms of low molecular weight heparin, p 5](#).

**Comment:** None.

**OPTION** LOW MOLECULAR WEIGHT HEPARIN

### Mortality

*Compared with unfractionated heparin* Low molecular weight heparin (LMWH) may be no more effective at reducing mortality at 5 days to 3 months (high-quality evidence).

### MI

*Compared with unfractionated heparin* LMWH is more effective at reducing MI at 5 days to 3 months (high-quality evidence).

### Cardiovascular events

*Compared with no heparin* LMWH is more effective at reducing the combined outcome of death or MI when given up to day 7, but is not more effective when given up to day 90. (moderate-quality evidence)

**Bleeding**

*Compared with no heparin* LMWH may not increase the risk of major bleeding when given up to day 7, but may increase the risk of major bleeding when given up to day 90. (low-quality evidence).

*Compared with unfractionated heparin* LMWH does not increase the risk of major bleeding at 5 days to 3 months (high-quality evidence).

**For GRADE evaluation of interventions for acute coronary syndrome, see [table, p 13](#).**

**Benefits:****LMWH versus no LMWH:**

We found one systematic review (search date not stated, 2 RCTs, 1639 people) comparing LMWH versus placebo or no heparin treatment in people with acute coronary syndrome (ACS).<sup>[12]</sup> LMWH was given for less than 7 days. It found that LMWH reduced the combined outcome of death or MI compared with control at the end of the treatment period (AR 13/809 [2%] with LMWH v 43/830 [5%] with placebo; OR 0.34, 95% CI 0.20 to 0.58). The systematic review identified five RCTs (12,099 people) comparing longer-term LMWH (from 7–90 days) versus placebo. It found that LMWH did not reduce death or MI at 90 days compared with placebo (AR 228/5453 [4%] with LMWH v 257/6646 [3%] with placebo; OR 0.98, 95% CI 0.81 to 1.17).

**LMWH versus unfractionated heparin:**

We found one systematic review (search date 2000; 7 RCTs, 11,092 people) comparing LMWH versus unfractionated heparin in people with ACS.<sup>[13]</sup> The two largest RCTs used enoxaparin as LMWH (2 RCTs, 7045 people). It found that LMWH significantly reduced MI compared with unfractionated heparin at 5 days to 3 months (AR 233/5580 [4%] with LMWH v 276/5512 [5%] with unfractionated heparin; RR 0.83, 95% CI 0.70 to 0.99). However, it found no significant difference between treatments in mortality or recurrent angina at 5 days to 3 months (mortality: AR 150/5580 [3%] with LMWH v 155/5512 [3%] with unfractionated heparin; RR 1.0, 95% CI 0.7 to 1.4; recurrent angina: 6 RCTs, 7209 people: 516/3642 [14%] with LMWH v 576/3576 [16%] with unfractionated heparin; RR 0.83, 95% CI 0.68 to 1.02).

**Harms:****LMWH versus no LMWH:**

The systematic review found that LMWH did not significantly increase major bleeding compared with placebo or no treatment at 7 days (OR 1.48, 95% CI 0.45 to 4.84, absolute numbers not reported). However, long-term LMWH significantly increased the risk of major bleeding compared with placebo or no treatment at 90 days (OR 2.26, 95% CI 1.63 to 3.14, absolute numbers not reported) equivalent to an excess of 12 bleeds for every 1000 people treated.<sup>[12]</sup>

**LMWH versus unfractionated heparin:**

The systematic review found no significant difference between LMWH and unfractionated heparin in major bleeding at 5 days to 3 months (AR 156/5550 [3%] with LMWH v 153/5472 [3%] with unfractionated heparin; RR 1.0, 95% CI 0.80 to 1.24)<sup>[13]</sup> (see [harms of unfractionated heparin, p 5](#)).

**Comment:**

LMWH, more specifically enoxaparin, may be a more reasonable alternative to unfractionated heparin for routine short-term use, given its similar safety profile to heparin and reduction in composite mortality or MI. Coagulation monitoring is not required and it can be self-administered after discharge.

**OPTION****DIRECT THROMBIN INHIBITORS****Cardiovascular events**

*Compared with unfractionated heparin* Direct thrombin inhibitors are more effective at reducing the combined outcome of death or MI at 30 days in people with acute coronary syndrome (moderate-quality evidence).

**Bleeding**

*Compared with unfractionated heparin* Direct thrombin inhibitors are more effective at reducing the risk of major bleeding (moderate-quality evidence).

**For GRADE evaluation of interventions for acute coronary syndrome, see [table, p 13](#).**

**Benefits:****Direct thrombin inhibitors versus unfractionated heparin:**

We found one systematic review (search date not stated, 11 RCTs, 35,070 people) comparing 7 days' treatment with direct thrombin inhibitors (hirudin, argatroban, bivalirudin, efegatran, inogatran) versus unfractionated heparin.<sup>[14]</sup> It found that direct thrombin inhibitors significantly reduced the combined outcome of death or MI compared with unfractionated heparin at 30 days (AR 7% with direct thrombin inhibitors v 8% with unfractionated heparin; RR 0.91, 95% CI 0.84 to 0.99).

- Harms:** **Direct thrombin inhibitors versus unfractionated heparin:**  
The systematic review found that direct thrombin inhibitors significantly reduced major bleeding during treatment compared with unfractionated heparin (AR 1.9% with direct thrombin inhibitors v 2.3% with heparin; OR 0.75, 95% CI 0.65 to 0.87). It found no significant difference in stroke between groups at 30 days (AR 0.5% with direct thrombin inhibitors v 0.5% with heparin; OR 1.01, 95% CI 0.78 to 1.31).<sup>[14]</sup>
- Comment:** **Clinical guide:**  
In heparin-allergic patients, direct thrombin inhibitors may produce similar clinical results, possibly with less death, MI, and bleeding. There was significant heterogeneity of RCTs in the systematic review, and different results were observed for the various agents.

OPTION	WARFARIN
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**Cardiovascular events**

*Compared with aspirin alone* Warfarin plus aspirin is no more effective at reducing the combined outcomes including mortality, MI, recurrent angina, or stroke at 12 weeks to 1 year in people with acute coronary syndrome (high-quality evidence)

**Bleeding**

*Compared with standard treatment* Adding warfarin increases the risk of major bleeding at 5 months (high-quality evidence).

For GRADE evaluation of interventions for acute coronary syndrome, see [table, p 13](#).

- Benefits:** **Warfarin plus aspirin versus aspirin alone:**  
We found no systematic review. We found five RCTs comparing warfarin plus usual treatment versus usual treatment alone.<sup>[15] [16] [17] [18]</sup> Two of the RCTs were reported in the same journal article.<sup>[16]</sup> The first RCT (214 people) compared warfarin plus aspirin versus aspirin alone.<sup>[15]</sup> It found that warfarin (target international normalised ratio [INR] 2.0–2.5) plus aspirin reduced the combined outcome of death, MI, or recurrent angina at 12 weeks compared with aspirin alone, but the difference did not reach significance (AR 13% with warfarin plus aspirin v 25% with aspirin alone;  $P = 0.06$ ). The second RCT (309 people) compared warfarin (fixed dose 3 mg/day) plus aspirin versus aspirin alone.<sup>[16]</sup> It found no significant difference between warfarin plus aspirin and aspirin alone in the combined outcome of death, MI, or recurrent angina at 6 months (AR 7% with warfarin plus aspirin v 4% with aspirin alone; RR 1.66, 95% CI 0.62 to 4.44).<sup>[16]</sup> The third RCT (197 people) compared warfarin (target INR 2.0–2.5) plus aspirin versus aspirin alone.<sup>[16]</sup> It found no significant difference between treatments in the combined outcome of death, MI, or recurrent angina at 6 months (AR 5% with warfarin plus aspirin v 12% with aspirin alone; RR 0.42, 95% CI 0.15 to 1.15). The fourth RCT (3712 people) compared adding warfarin (target INR 2.0–2.5) to standard treatment versus standard treatment alone.<sup>[17]</sup> Standard treatment for most participants included aspirin; use of aspirin at 5 months was significantly higher among the group receiving standard treatment alone than in group receiving warfarin plus standard treatment (AR 83% in the warfarin group and 93% in the standard treatment group;  $P$  less than 0.001). The RCT found no significant difference between treatments in the combined outcome of death, MI, and stroke after 5 months (8% with warfarin v 8% with standard treatment alone; RR 0.90, 95% CI 0.72 to 1.14).<sup>[17]</sup> The fifth RCT (135 people with prior CABG) compared warfarin plus aspirin, warfarin plus placebo, and aspirin plus placebo.<sup>[18]</sup> It found no significant difference between treatments in the combined outcome of death, MI, or hospital admission for unstable angina after 1 year (AR 11% with warfarin plus aspirin v 14% with warfarin plus placebo v 12% with aspirin plus placebo;  $P = 0.76$  for overall comparison of the three treatment groups).<sup>[18]</sup>

- Harms:** **Warfarin plus aspirin versus aspirin alone:**  
In the fourth RCT, adding warfarin to standard treatment increased major bleeding compared with standard treatment alone (AR 3% with warfarin plus standard treatment v 1% with standard treatment alone; RR 1.99, 95% CI 1.23 to 3.22; NNH 71; CI not reported).<sup>[17]</sup>

- Comment:** **Clinical guide:**  
In people with a high risk of thromboembolic events (i.e. those with atrial fibrillation, prosthetic heart valves, intracardiac thrombi, recurrent thromboembolic events, or anti-phospholipid syndrome), continuing warfarin should be at clinical discretion. If warfarin is to be used as part of the treatment regimen, then the target INR for greatest benefit seems to be between 2 and 3. Warfarin should be withheld in people who have invasive therapy as it increases bleeding at the time of catheterisation.

<b>QUESTION</b>	What are the effects of anti-ischaemic treatments in people with acute coronary syndrome?
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<b>OPTION</b>	<b>BETA-BLOCKERS</b>
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**Mortality**

*Compared with placebo* We don't know what effect beta-blockers have on mortality in people with acute coronary syndrome ([low-quality evidence](#)).

**MI**

*Compared with placebo* We don't know what effect beta-blockers have on MI in people with acute coronary syndrome ([low-quality evidence](#)).

**For GRADE evaluation of interventions for acute coronary syndrome, see [table, p 13](#).**

**Benefits:****Beta-blockers versus placebo:**

We found two RCTs. <sup>[19]</sup> <sup>[20]</sup> The first RCT (338 people with rest angina not already receiving a beta-blocker) compared metoprolol versus placebo. <sup>[19]</sup> It found no significant difference between metoprolol and placebo in MI at 48 hours (16% with metoprolol v 15% with placebo; RR 1.07, 95% CI 0.54 to 2.09; absolute numbers not reported). The second RCT (81 people with unstable angina on "optimal doses" of nitrates and nifedipine) compared propranolol (at least 160 mg/day) versus placebo. <sup>[20]</sup> It found no significant difference in mortality between propranolol and placebo at 30 days (6/42 [14%] with propranolol v 3/39 [8%] with placebo, reported as not significant; RR, P value and 95% CI not reported). People taking propranolol had a lower cumulative probability of experiencing recurrent rest angina at 30 days (results presented graphically; P = 0.013).

**Harms:****Beta-blockers versus placebo:**

The first RCT gave no information on harms. The second RCT reported that bradycardia and hypotension were each reported by one person who received propranolol (1/42 with propranolol, rate in control group and significance data not reported). Potential adverse effects of beta-blockers in any patient population include bradycardia, exacerbation of reactive airways disease, and hypoglycaemia in people with diabetes.

**Comment:**

We found no good evidence that beta-blockers prevent death or MI in the first 6 months after an acute coronary syndrome (unstable angina or non-ST elevation MI). Consensus suggests that, until further data are available, intravenous nitrates remain the preferred treatment for symptom control in ACS patients.

<b>OPTION</b>	<b>NITRATES</b>
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**Adverse effects**

*Compared with placebo* Nitrates increase the risk of headache or drop in blood pressure ([high-quality evidence](#)).

**Note:**

We found no direct information about nitrates in the reduction of mortality or MI in people with acute coronary syndrome.

**For GRADE evaluation of interventions for acute coronary syndrome, see [table, p 13](#).**

**Benefits:****Nitrates versus placebo:**

We found two RCTs. <sup>[21]</sup> <sup>[22]</sup> The first RCT (162 people with non-ST elevation MI) compared intravenous glyceryl trinitrate versus placebo for 48 hours. <sup>[21]</sup> It found that glyceryl trinitrate significantly reduced the proportion of people with more than two episodes of chest pain or one new episode lasting more than 20 minutes (18% with glyceryl trinitrate v 36% with placebo; RR 0.50, 95% CI 0.25 to 0.90), and the proportion of people needing more than two additional sublingual glyceryl trinitrate tablets (16% with glyceryl trinitrate v 31% with placebo; RR 0.52, 95% CI 0.26 to 0.97). The second RCT (200 people hospitalised for unstable angina within 6 months of PTCA) compared intravenous glyceryl trinitrate alone, heparin alone, glyceryl trinitrate plus heparin, and placebo. <sup>[22]</sup> It found that recurrent angina occurred significantly less frequently in people treated with glyceryl trinitrate alone or glyceryl trinitrate plus heparin compared with placebo, but there was no benefit from heparin alone over placebo or additional benefit from combination treatment compared with glyceryl trinitrate alone (AR 43% with glyceryl trinitrate alone v 42% with glyceryl trinitrate plus heparin v 75% with heparin alone v 75% with placebo; P less than 0.003 for glyceryl trinitrate alone and for glyceryl trinitrate plus heparin v placebo; P values for other comparisons not reported).

**Harms:****Nitrates versus placebo:**

The first RCT found that intravenous glyceryl trinitrate (GTN) significantly increased adverse effects (headache or drop in blood pressure by more than 20%) compared with placebo (7/73 [10%] with

## Acute coronary syndrome (unstable angina and non-ST elevation MI)

glyceryl trinitrate v 0/70 [0%] with placebo; P less than 0.001) The second RCT gave no information on harms. A potential adverse effect of nitrates is symptomatic hypotension. Both older and more recent large RCTs in people with other ischaemic conditions showed that nitrates were safe and well tolerated when used judiciously in clinically appropriate doses.

**Comment:** We found no good evidence that nitrates prevent death or MI, although consensus suggests that, until further data are available, intravenous nitrates remain the preferred treatment for symptom control in people with ACS.

OPTION	CALCIUM CHANNEL BLOCKERS
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**Mortality**

*Compared with placebo* Calcium channel blockers are no more effective at reducing mortality in people with unstable angina at 48 hours to 5 months ([moderate-quality evidence](#)).

*Compared with beta-blockers* Calcium channel blockers are no more effective at reducing mortality in people with unstable angina at 48 hours to 5 months ([moderate-quality evidence](#)).

**MI**

*Compared with placebo* Calcium channel blockers are no more effective at reducing MI in people with unstable angina at 48 hours to 5 months ([moderate-quality evidence](#)).

*Compared with beta-blockers* Calcium channel blockers are no more effective at reducing MI in people with unstable angina at 48 hours to 5 months ([moderate-quality evidence](#)).

**Note**

Short-acting calcium channel blockers (such as nifedipine) have been associated with increased mortality in people with CHD.

**For GRADE evaluation of interventions for acute coronary syndrome, see [table, p 13](#).**

**Benefits:**

We found one systematic review (search date not reported, 6 RCTs, 1109 people with unstable angina) <sup>[23]</sup> comparing calcium channel blockers versus either a beta-blocker (propranolol, 3 RCTs) or placebo (3 RCTs). <sup>[19]</sup> The review found that mortality and rates of MI were similar between calcium channel blockers and both placebo and propranolol at 48 hours to 5 months, but did not report significance (placebo-controlled trials: mortality AR 8/439 with calcium channel blockers v 7/427 with placebo; MI 89/409 with calcium channel blockers v 89/397 with placebo; propranolol-controlled trials: mortality 6/152 with calcium channel blockers v 2/151 with propranolol; MI 21/152 with calcium channel blockers v 15/151 with propranolol; P values not reported). The review found no significant difference between calcium channel blockers and both controls combined in mortality or MI at 48 hours to 5 months (mortality: 14/591 [2%] with calcium channel blockers v 9/578 [2%] with control; MI: 110/561 [20%] with calcium channel blockers v 104/548 [19%] with control; ORs and 95% CIs presented graphically). One RCT included in the systematic review compared nifedipine, metoprolol, or both, versus placebo. <sup>[19]</sup> It found no difference between nifedipine and placebo in MI, or combined MI and recurrent ischaemia at 48 hours (MI: RR 1.51, 95% CI 0.87 to 2.74; combined MI and recurrent ischaemia: RR 1.15, 95% CI 0.83 to 1.64; absolute numbers not reported). It found that nifedipine significantly increased combined MI and recurrent ischaemia when compared with metoprolol at 48 hours (RR 0.66, 95% CI 0.43 to 0.98; absolute numbers not reported). <sup>[19]</sup>

**Harms:**

The systematic review gave no information on harms. Observational studies have reported increased mortality with short-acting dihydropyridine calcium channel blockers (such as nifedipine) in people with CHD. <sup>[24]</sup> <sup>[25]</sup>

**Comment:** We found no good evidence that calcium channel blockers prevent death or MI.

QUESTION	What are the effects of lipid-lowering treatments in people with acute coronary syndrome?
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OPTION	STATINS	New
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**Cardiovascular events**

*Compared with placebo* Statins are no more effective at reducing the combined outcome of mortality or MI at 16 weeks ([moderate-quality evidence](#)).

**For GRADE evaluation of interventions for acute coronary syndrome, see [table, p 13](#).**

## Acute coronary syndrome (unstable angina and non-ST elevation MI)

- Benefits:** **Statins versus placebo:**  
We found one RCT (3086 people within 24–96 hours of acute coronary syndrome) comparing 80 mg of atorvastatin versus placebo. <sup>[26]</sup> It found no significant difference in the combined outcome of mortality or non-fatal MI at 16 weeks (AR 155/1538 [10%] with atorvastatin v 169/1548 [11%] with placebo; RR 0.92, 95% CI 0.75 to 1.13). However, it found that atorvastatin significantly reduced emergency hospitalisation for recurrent myocardial ischaemia compared with placebo at 16 weeks (AR 95/1538 [6%] with atorvastatin v 130/1548 [8%] with placebo; RR 0.74, 95% CI 0.57 to 0.95).
- Harms:** **Statins versus placebo:**  
The RCT found that atorvastatin significantly increased the proportion of people with abnormal liver transaminase levels (at 3 times the upper limit of normal) compared with placebo at 16 weeks (AR 38/1538 [3%] with atorvastatin v 9/1548 [1%] with placebo; P less than 0.001). Three of the people with abnormal LFTs from the atorvastatin group were hospitalised with a diagnosis of hepatitis. No one in either group was reported to have myositis. <sup>[26]</sup>
- Comment:** This RCT is likely to be underpowered to reliably estimate the effects of statins on mortality and MI over this short period. However, there seems to be little harm in starting statins for secondary prevention on presentation. There is stronger evidence that statins improve clinical outcomes in the long term (see review on secondary prevention of ischaemic cardiac events).

QUESTION	What are the effects of invasive treatments in people with acute coronary syndrome?
OPTION	ROUTINE EARLY CARDIAC CATHETERISATION AND REVASCULARISATION

**Mortality**

*Compared with medical management or delayed surgical revascularisation* Routine early surgical revascularisation may reduce mortality at 1–60 months in people with non-ST elevation MI (low-quality evidence).

**MI**

*Compared with medical management or delayed surgical revascularisation* Routine early surgical revascularisation may be more effective at reducing MI at 1–60 months in people with non-ST elevation MI (low-quality evidence).

**Bleeding**

*Compared with medical management or delayed surgical revascularisation* Routine early surgical revascularisation may increase the risk of major bleeding (moderate-quality evidence).

**For GRADE evaluation of interventions for acute coronary syndrome, see table, p 13 .**

- Benefits:** **Routine early cardiac catheterisation and revascularisation versus more conservative strategies:**  
We found one systematic review <sup>[27]</sup> (7 RCTs, 8375 people) comparing routine early percutaneous coronary intervention (PCI) with more conservative strategies in patients with non-ST elevation MI. <sup>[27]</sup> Six of the RCTs identified compared early PCI versus medical management. A proportion of the medical management groups went on to have later PCI in all of the trials. The remaining RCT in the review compared immediate (within 6 hours) versus late (between 72–120 hours) PCI. The review found that routine early PCI significantly reduced mortality and non-fatal MI at 1–60 months compared with more conservative strategies (mortality: 5% with early PCI v 7% with more conservative strategies; RR 0.75, 95% CI 0.63 to 0.90; P = 0.001; non-fatal MI: 8% with early PCI v 9% with more conservative strategies; RR 0.83, 95% CI 0.72 to 0.96; P = 0.012; absolute numbers not reported). It also found that early PCI significantly reduced the proportion of people readmitted to hospital with unstable angina compared with more conservative strategies at 6–60 months (AR 20% with early PCI v 29% with more conservative strategies; RR 0.69, 95% CI 0.65 to 0.74; P = 0.0001; absolute numbers not reported).
- Harms:** **Routine early cardiac catheterisation and revascularisation versus more conservative strategies:**  
The systematic review gave no information on harms. One RCT from the systematic review (2457 people with non-ST elevation MI) found that early invasive treatment increased major bleeding, but not stroke, compared with non-invasive treatment (major bleeds: AR 2% with invasive treatment v 1% with non-invasive treatment; NNH 111; 95% CI not reported). <sup>[28]</sup> A second RCT from the systematic review (2220 people with non-ST elevation MI) found that cardiac catheterisation increased bleeding compared with standard treatment (6% with cardiac catheterisation v 3% with standard treatment; P less than 0.01; NNH 34; 95% CI not reported). <sup>[29]</sup>
- Comment:** The systematic review suggests that revascularisation may be key in improving late outcomes, and that the timing of the procedure may be less important. Adjuvant glycoprotein IIb/IIIa treatment

may enhance the safety of PCI by decreasing MI and death. Early invasive therapy improves survival but does increase the risk of bleeding. Continued attempts to decrease major bleeding during PCI remain a priority.

## GLOSSARY

**International normalised ratio (INR)** A value derived from a standardised laboratory test that measures the effect of an anticoagulant. The laboratory materials used in the test are calibrated against internationally accepted standard reference preparations, so that variability between laboratories and different reagents is minimised. Normal blood has an international normalised ratio of 1.0. Therapeutic anticoagulation often aims to achieve an international normalised ratio value of 2.0–3.5.

**High-quality evidence** Further research is very unlikely to change our confidence in the estimate of effect.

**Low-quality evidence** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Moderate-quality evidence** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

## SUBSTANTIVE CHANGES

**Statins** One RCT added comparing atorvastatin versus placebo in people within 24–96 hours of acute coronary syndrome.<sup>[26]</sup> It found no significant difference in combined mortality or non-fatal MI at 16 weeks. It found that atorvastatin significantly reduced emergency re-hospitalisation for myocardial ischaemia at 16 weeks.

**Glycoprotein IIb/IIIa inhibitors** One systematic review added comparing glycoprotein IIb/IIIa inhibitors versus placebo in people with acute coronary syndrome, who were not due for routine invasive treatment. It found that glycoprotein IIb/IIIa inhibitors significantly reduced the combined outcome of death and MI at 30 days.

**Routine early cardiac catheterisation and revascularisation** One systematic review added comparing routine early cardiac catheterisation and revascularisation versus more conservative management.<sup>[27]</sup> It found that routine early cardiac catheterisation and revascularisation significantly reduced the combined outcome of mortality and non-fatal MI.

**Clopidogrel** Evidence re-evaluated; categorisation changed (Beneficial) in light of high-quality evidence demonstrating a reduction in the combined outcome of death, MI, and stroke with clopidogrel versus placebo at 30 days.<sup>[6]</sup>

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**TABLE** GRADE evaluation of interventions for acute coronary syndrome

Important outcomes		Mortality, MI, adverse effects							
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of antiplatelet treatments in people with acute coronary syndrome?									
12 (5031) <sup>[5]</sup>	Cardiovascular events	Aspirin v placebo	4	0	0	−1	0	Moderate	Directness point deducted for inclusion of different interventions
12 (5031) <sup>[5]</sup>	Bleeding	Aspirin v placebo	4	0	0	−1	0	Moderate	Directness point deducted for inclusion of different interventions
1 (12,562) <sup>[6]</sup>	Cardiovascular events	Clopidogrel v placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (12,562) <sup>[6]</sup>	Bleeding	Clopidogrel v placebo	4	0	0	0	0	High	
What are the effects of antithrombin treatments in people with acute coronary syndrome?									
6 (31,402) <sup>[10]</sup>	Cardiovascular events	Intravenous glycoprotein IIB/IIIA inhibitors v placebo	4	0	0	−2	0	Low	Directness points deducted for high use of surgery in participants, and not using other standard medical treatments by current practice
6 (31,402) <sup>[10]</sup>	Bleeding	Intravenous glycoprotein IIB/IIIA inhibitors v placebo	4	0	0	−1	0	Moderate	Directness point deducted for not using current standard medical treatments
6 (1353) <sup>[11]</sup> <sup>[12]</sup>	Cardiovascular events	Unfractionated heparin plus aspirin v aspirin alone	4	0	−1	0	0	Moderate	Consistency point deducted for different results at different times
1 (1353) <sup>[11]</sup>	Bleeding	Unfractionated heparin plus aspirin v aspirin alone	4	−1	0	0	0	Moderate	Quality point deducted for sparse data due to low event rate
7 (13,738) <sup>[12]</sup>	Cardiovascular events	LMWH v no heparin	4	0	−1	0	0	Moderate	Consistency point deducted for different results at different times
7 (13,738) <sup>[12]</sup>	Bleeding	LMWH v no heparin	4	−1	−1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for different results at different times
7 (11,092) <sup>[13]</sup>	Mortality	LMWH v unfractionated heparin	4	0	0	0	0	High	
7 (11,092) <sup>[13]</sup>	MI	LMWH v unfractionated heparin	4	0	0	0	0	High	
7 (11,092) <sup>[13]</sup>	Bleeding	LMWH v unfractionated heparin	4	0	0	0	0	High	
11 (35,070) <sup>[14]</sup>	Cardiovascular events	Direct thrombin inhibitors v unfractionated heparin	4	0	−1	0	0	Moderate	Consistency point deducted for heterogeneity of RCTs
11 (35,070) <sup>[14]</sup>	Bleeding	Direct thrombin inhibitors v unfractionated heparin	4	0	−1	0	0	Moderate	Consistency point deducted for heterogeneity of RCTs
5 (4567) [11, 12, 13, 14]	Cardiovascular events	Warfarin v no warfarin	4	0	0	−1	0	Moderate	Directness point deducted for different definitions of combined outcome
1 (3712) [13]	Bleeding	Warfarin v no warfarin	4	0	0	0	0	High	
What are the effects of anti-ischaemic treatments in people with acute coronary syndrome?									

Important outcomes		Mortality, MI, adverse effects							
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
1 (338) [15]	MI	Beta-blockers v placebo	4	−2	0	0	0	Very low	Quality points deducted for incomplete reporting of results and short follow-up. Directness point deducted for narrow range of beta-blockers studies
1 (81) [16]	Mortality	Beta-blockers v placebo	4	−2	0	0	0	Very low	Quality points deducted for incomplete reporting of results and short follow-up. Directness point deducted for narrow range of beta-blockers studies
1 (162) [17]	Adverse effects	Nitrate v placebo	4	0	0	0	0	High	
6 (856) [19]	Mortality	Calcium channel blockers v placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
6 (856) [19]	MI	Calcium channel blockers v placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
6 (303) [19]	Mortality	Calcium channel blockers v beta-blockers	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
6 (303) [19]	MI	Calcium channel blockers v beta-blockers	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
What are the effects of lipid-lowering treatments in people with acute coronary syndrome?									
1 (3086) [22]	Mortality or MI	Statins v placebo	4	0	0	−1	0	High	Directness point deducted for narrow range of interventions studied
What are the effects of invasive treatments in people with acute coronary syndrome?									
7 (8375) [23]	Mortality	Routine early surgical revascularisation v more conservative management	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for inclusion of different interventions
7 (8375) [23]	MI	Routine early surgical revascularisation v more conservative management	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for inclusion of different interventions
2 (4677) [24, 25]	Bleeding	Routine early surgical revascularisation v more conservative management	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
Type of evidence: 4 = RCT; 2 = Observational									
Consistency: similarity of results across studies									
Directness: generalisability of population or outcomes									
Effect size: based on relative risk or odds ratio									